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REMARKS

1. Interview Conducted February 19, 2008.

Applicant thanks the Examiner and her supervisor for their time on February 19, 2008. Applicant also appreciated the various claim amendments suggested by the Examiner that, if accepted, would put the existing claim set in condition for allowance.

2. Rejection of Claims 1-21 under 35 U.S.C. 112, first paragraph.

The rejection of Claims 1-21 was maintained under 35 U.S.C. 112, first paragraph because the specification allegedly fails to enable the prevention of kidney disease for the reasons of record. In particular, the Examiner is of the opinion that the term, "prevent" means that no disease will ever be found in a patient after administration of a particular therapeutic. Specifically, she states in the recent Advisory Action dated December 26, 2007 that, [a]ccordingly, treatment with 2-OHE shows decreases in various markers for kidney disease, but does not show total prevention of the disease from ever occurring. Applicant specifically makes of record that it does not in any way agree with the Examiner's rejections of record on this point.

In order to expedite allowance of claims, and without prejudice or disclaimer of the subject matter thereof, Applicant has amended Claims 1, 5, 9, 13, and 21 to exclude the term, "preventing". In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of Claims 1 - 21 under 35 U.S.C. 112, first paragraph.

3. Rejection of Claims under 35 U.S.C. 103(a)

In the Final Office Action the Examiner introduced new argumentation as to why, in general, the rejections of claims under 35 U.S.C. 103(a) were proper. Applicant reiterates its reply below for the sake of convenience as it does not feel its arguments have been responded to by the Examiner to date. Additionally, after the reiteration of the previously filed arguments, Applicant presents additional arguments and clarifications previously presented during the telephonic interview of February 19, 2008.

a. Arguments Of Record in Last-Filed Response

Applicant's prior arguments are still deemed responsive and explanatory to the rejection and are included in their entirety below, but in addition to those arguments, Applicant has additional grounds for dispute with these rejections. Without any citation to reference, the Examiner claims that it would be obvious to one of skill in the art that a disclosure that suggests treating "nephropathies" would somehow lead to the treatment of a drug induced kidney disease. This statement suggests the Examiner has not actually read the later Tofovic reference as well as the patent application, both of which suggest why one of skill in the art could not make such a leap of faith and why, in the view of the inventors (and their peers), the later experiments to prove 2-OHE was directly renoprotective were still necessary even in light of their own earlier results.

The abstract cited by the examiner, published by the inventors, merely showed that 2-OHE "attenuates the development of renal disease in genetic nephropathy associated with obesity and the metabolic syndrome." (Tofovic, *J Am Soc Nephrol*, 13:2737, 2002). The inventors believed that further studies were needed to show that 2-OHE "exerts direct renoprotective effects *in vivo*," (Tofovic, 2002), and it is the requirement for these new studies that directly contradicts the Examiner's uncited and unsupported conclusory statements regarding the obviousness of this invention in light of the inventor's prior published work. Therefore, Applicant contends that Examiner should show at least one reference that supports the conclusion that teachings about attenuation of a genetic disease somehow makes obvious to one of skill in the art claims to preventing drug induced kidney disease. The examiner's line of reasoning here would make any disease treatment or prevention obvious in light of mouse genetic models, and yet the office continually maintains that genetic models are insufficient to enable human therapies because the genetic animals models lack the connection to real life syndrome. It appears that in this instance, the Examiner is saying the exact reverse, that a genetic model somehow makes obvious any other model and any other disease. That simply does not comport with logic or recent practice at the U.S.P.T.O. regarding the validity of genetic animal models.

In regards to the Xiao reference, the Examiner did not even address Applicant's prior arguments made against this reference. As reminded by Applicant in the last response, the Examiner must at least make an effort to address Applicant's arguments. MPEP 707.07(f) clearly states that even when the Examiner finds Applicant's prior arguments to be moot, "the examiner must, however, address any arguments presented by the applicant which are still relevant to any references being applied." Instead, Examiner restated Applicant's argument and then moved on

to her discussion of the Allison reference. It is Applicant's contention that neither Tofovic nor Xiao is a valid obviousness rejection, and therefore there is no need to even address Allison in light of either reference.

b. Newly Presented Arguments and Clarifications

During the telephonic interview of February 19, 2008, there appeared to be a technical misunderstanding as to the physiological distinction between general nephropathies and drug-induced nephrotoxicity. The pathologies of both conditions were explained in detail to the Examiner and her supervisor and the distinctions between the two. All references of record were also discussed at length. As a result of this discussion, and merely to expedite prosecution, Applicant herein amends Claims 1, 5, 9, 13 and 21 to limit the claims to "PAN" as a specific form of drug inducement without prejudice or disclaimer of the subject matter therein. Applicant specifically makes of record that it does not in any way agree with the Examiner's rejections of record on this point.

As such, Applicant's believe all of the Rejections under 35 U.S.C. 103(a) are improper and respectfully request that at this point they be removed and the claims be allowed. Applicant's arguments above are responsive to prior arguments made by the Examiner and are sufficient to explain to the Examiner why the cited references are insufficient to make the invention obvious.

4. Rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a)

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 were rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. "Renoprotective effects of 2-hydroxyestradiol," *J Am Soc Nephrol* 12: 86A, 2001, for the reasons of record. Applicant reiterates its reply below for the sake of convenience as it does not feel its arguments have been responded to by the Examiner to date. Additionally, after the reiteration of the previously filed arguments, Applicant presents additional arguments and clarifications previously presented during the telephonic interview of February 19, 2008.

a. Arguments Of Record in Last-Filed Response

Applicant again point out that in order for an Examiner to establish a prima facie case of obviousness, the Examiner must show that each and every one of the claim limitations was

suggested or taught by the prior art being relied upon. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). When an independent claim is deemed nonobvious under 35 U.S.C. 103, then all claims depending therefrom are nonobvious as well. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicant respectfully submits that the Examiner has not overcome this burden. Specifically, all of the claims that were rejected by the Examiner recite that the conditions being "prevented" or treated are "drug-induced." Tofovic et al does not teach that the conditions being treated are drug-induced nor does Tofovic et al teach the prevention of such drug-induced conditions. Accordingly, the Examiner has not overcome the aforementioned burden since each and every one of the claim limitations of the instant invention were not taught or suggested by Tofovic et al.

Furthermore, the Examiner has the burden to prove that the prior art relied upon contains some suggestion or incentive that would motivate the skilled artisan to modify a reference. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001). Applicant submits that the Examiner has not satisfied this burden. All of the claims rejected by the Examiner in this office action contemplate preventing various drug-induced conditions. Tofovic et al does not suggest modifying its teachings in order to prevent the conditions mentioned nor does Tofovic et al suggest that its teachings would also be effective in treating or preventing drug-induced conditions. Therefore, Applicant respectfully submits that the Examiner has failed to show that Tofovic et al contains some suggestion or incentive to modify its teachings in order to prevent the conditions or prevent or treat the drug-induced conditions of the instant application.

Also, the Examiner has the burden of proving that the proposed modification of the prior art has a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Applicant submits that the Examiner has not satisfied this burden. The Examiner stated in the 35 U.S.C. 112, first paragraph rejection beginning on page 2 of this Office Action that this case involves "an unpredictable and undeveloped art." (See (5) on page 4 of the instant Office Action). Therefore, Applicant fails to see how a person of ordinary skill in the art would have a reasonable expectation of success in modifying Tofovic et al

to prevent the conditions of the instant application nor treat or prevent the drug-induced conditions of the instant application. If the field of the instant invention is unpredictable as the Examiner submitted, a skilled artisan would not have a reasonable expectation of success in modifying Tofovic et al to prevent the conditions of the instant application nor would the skilled artisan have a reasonable expectation of success in treating or preventing the drug-induced conditions of the instant application.

In regard to claims 1, 2, 9, 13, 17 and 21, the Examiner argued that it is obvious that the teachings of Tofovic et al would treat the conditions listed in the above claims. However, with the statement made by the Examiner that this case involves "an unpredictable and undeveloped art," absent some motivation or suggestion found in Tofovic et al to modify its teachings, Applicant submits that it would not be obvious that its teachings would treat the conditions listed in the aforementioned claims.

Moreover, the Examiner stated that it is obvious that the teachings of Tofovic et al would "treat" the conditions listed in claims 1, 2, 9, 13, 17 and 21 but the Examiner did not discuss how it is obvious that the teachings of Tofovic et al would prevent the conditions listed in the claims. Since the claims rejected by the Examiner contemplate treating or preventing, the Examiner has not established that each and every one of the claim limitations of the instant invention were taught or suggested by Tofovic et al.

b. Newly Presented Arguments and Clarifications

During the telephonic interview of February 19, 2008, there appeared to be a technical misunderstanding as to the physiological distinction between general nephropathies and drug-induced nephrotoxicity. The pathologies of both conditions were explained in detail to the Examiner and her supervisor and the distinctions between the two. All references of record were also discussed at length. As a result of this discussion, and merely to expedite prosecution, Applicant herein amends Claims 1, 5, 9, 13 and 21 to limit the claims to "PAN" as a specific form of drug inducement without prejudice or disclaimer of the subject matter therein. Applicant specifically makes of record that it does not in any way agree with the Examiner's rejections of record on this point.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a).

5. Rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a)

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 were rejected under 35 U.S.C. 103(a) as being unpatentable over Xiao, S. et al. "Effects of estradiol and its metabolites on glomerular endothelial nitric oxide synthesis and mesangial cell growth," Hypertension, 2001; 37; 645-650, for the reasons of record. Applicant reiterates its reply below for the sake of convenience as it does not feel its arguments have been responded to by the Examiner to date. Additionally, after the reiteration of the previously filed arguments, Applicant presents additional arguments and clarifications previously presented during the telephonic interview of February 19, 2008.

a. Arguments Of Record in Last-Filed Response

Initially, Applicant respectfully submits that the Examiner mis-characterizes the teachings of Xiao et al. The Xiao et al reference teaches that "...estradiol stimulates endothelial cell-derived nitric oxide (NO) synthesis...," in paragraph 2 on page 645. Furthermore, that same paragraph goes on to explain that, "...decreased NO synthesis...is associated with the pathogenesis of renal diseases..." The end of that paragraph hypothesizes that, "...estradiol may...reduce the rate of progression of renal disease by stimulating NO synthesis..." The conclusion reached by Xiao et al., is stated in the final paragraph on page 649 as, "...estradiol may protect against the progression of renal disease by inducing NO synthesis in GECs and inhibiting GMC growth..." It should be noted that all of the aforementioned information relates to estradiol and not estradiol metabolites such as 2-OHE.

Very importantly, Xiao et al., teaches that "[t]reatment with estradiol, but not 2-hydroxyestradiol and 2-methoxyestradiol, induced nitric oxide synthesis. *See* Abstract. Since Xiao et al. concluded that, "...estradiol may protect against the progression of renal disease ***by inducing NO synthesis in GECs and*** inhibiting GMC growth..." it would logically follow that since Xiao et al. teaches that 2-hydroxyestradiol does not induce NO synthesis, it would not protect against the progression of renal disease. (Emphasis added) Accordingly, Applicant submits that Xiao et al. teaches away from the instant application and thus cannot properly be used by the Examiner as support for a 35 U.S.C. 103(a) rejection.

The Examiner has the burden to prove that, among other things, the prior art relied upon contains some suggestion or incentive that would motivate the skilled artisan to modify a reference. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001).

Applicant submits that the Examiner has not satisfied this burden. The Examiner argues that one having ordinary skill in the art would have been motivated to extend the findings of Xiao et al. to *in vivo* models of nephropathies to evaluate the renoprotective effects of these compounds. Applicant respectfully disagrees with Examiner's argument. Applicant submits that since Xiao et al. teaches that 2-OHE does not induce NO synthesis and thus will not protect against the progression of renal disease, one of ordinary skill in the art would have no motivation to extend those findings since they teach away from the disclosure of the instant invention.

Also, the Examiner has the burden of proving that the proposed modification of the prior art has a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Applicant submits that the Examiner has not satisfied this burden either. Since Xiao et al. teaches that 2-OHE does not induce NO synthesis and thus will not protect against the progression of renal disease, Applicant submits that one of ordinary skill in the art would have no expectation of success in protecting against the progression of renal disease *in vivo*, as suggested by the Examiner.

b. Newly Presented Arguments and Clarifications

During the telephonic interview of February 19, 2008, there appeared to be a technical misunderstanding as to the physiological distinction between general nephropathies and drug-induced nephrotoxicity. The pathologies of both conditions were explained in detail to the Examiner and her supervisor and the distinctions between the two. All references of record were also discussed at length. As a result of this discussion, and merely to expedite prosecution, Applicant herein amends Claims 1, 5, 9, 13 and 21 to limit the claims to "PAN" as a specific form of drug inducement without prejudice or disclaimer of the subject matter therein. Applicant specifically makes of record that it does not in any way agree with the Examiner's rejections of record on this point.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22 and 24 under 35 U.S.C. 103(a).

6. Rejection of Claims 3, 7, 11, 15, 19 and 23 under 35 U.S.C. 103(a)

Claims 3, 7, 11, 15, 19 and 23 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. and Xiao et al. as applied in the above rejections and in view of Allison (U.S. Pg-Pub 2006/0083778). Applicant reiterates its reply below for the sake of convenience as it does not feel its arguments have been responded to by the Examiner to date. Additionally, after the reiteration of the previously filed arguments, Applicant presents additional arguments and clarifications previously presented during the telephonic interview of February 19, 2008.

a. Arguments Of Record in Last-Filed Response

Specifically, the Examiner argues that Tofovic et al. and Xiao et al. do not teach a controlled release formulation but that Allison teaches a device that is capable of sustained release of the active ingredient. Accordingly, the Examiner argues, it would have been obvious to combine the teachings of Tofovic et al. and Xiao et al. with Allison.

The Examiner submitted that Tofovic et al and Xiao do not teach a controlled release formulation but as Applicant has pointed out in each of the previous 35 U.S.C. 103(a) rejection sections, there are many other things that those references do not teach. Illustratively, Tofovic et al does not teach preventing the conditions of the instant application nor does it teach treating or preventing the drug-induced conditions of the instant application. Further, Xiao actually teaches away from the instant invention because it teaches that 2-hydroxyestradiol does not induce NO synthesis thus it would not protect against the progression of renal disease. Since Xiao teaches away from the instant invention, it cannot properly be used in a 35 U.S.C. 103(a) rejection. Therefore, there is no motivation to combine these references with Allison because both Xiao and Tofovic are incorrectly cited as proper 35 U.S.C. 103(a) prior art.

As previously stated in this Response, the Examiner has the burden to show that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Even after combining Tofovic et al and Xiao et al with Allison, the Examiner has not satisfied the aforementioned burden since none of the references suggest or teach preventing the conditions of the instant invention nor do they teach or suggest treating or preventing the drug-induced conditions of the instant invention.

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b. Newly Presented Arguments and Clarifications

During the telephonic interview of February 19, 2008, there appeared to be a technical misunderstanding as to the physiological distinction between general nephropathies and drug-induced nephrotoxicity. The pathologies of both conditions were explained in detail to the Examiner and her supervisor and the distinctions between the two. All references of record were also discussed at length. As a result of this discussion, and merely to expedite prosecution, Applicant herein amends Claims 1, 5, 9, 13 and 21 to limit the claims to "PAN" as a specific form of drug inducement without prejudice or disclaimer of the subject matter therein. Applicant specifically makes of record that it does not in any way agree with the Examiner's rejections of record on this point.

7. Concluding Remarks

In view of the foregoing, Applicant respectfully submits that all rejections under 35 U.S.C. 112 and 35 U.S.C. 103(a) have been overcome. Accordingly, Applicant believes that Claims 1-24 are now in a condition for allowance. In the event the Examiner has any questions regarding the Applicant's position, a telephone call to the undersigned representative is requested.

Respectfully Submitted,

4/2/08
Date

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